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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/541,044	05/08/2006	Benjamin L Miller	176/61442	1984

7590 12/30/2009

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
12/30/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

CONTINUATION

1. The declaration under 35 USC 1.132 and remarks filed 11/23/2009 under 37 CFR 1.116 in reply to the final rejection have been thoroughly considered but have not found persuasive and are addressed below. The final office action with regard to the rejections of claims 1-24, 27-28, and 67-68 under 35 USC 103(a), and the rejection of claims 1-25, 27-28, 37, 42, 67-68 on the ground of nonstatutory obviousness-type double patenting mailed 05/04/2005, is maintained.

2. The terminal disclaimer filed 11/23/2009 has been approved. The rejection of claims 1-25, 27-28, 37, 42, 67-68 and claims 37-42 on the grounds of non-statutory obviousness-type double patenting of US Patent 7442510 is withdrawn in view of the filing of the terminal disclaimer.

3. The rejections of claims 25, 37, and 42 under 35 USC 103(a) is withdrawn in view of the arguments presented by applicant on page 5 of the response. Specifically SEQ ID NO 1 which contains a specific 9 nt 5' sequence and a specific 7 nt 3' sequence which is not suggested by the combination of references is found persuasive and the rejection is withdrawn.

4. The response traverses the rejection of claims 1-11, 14-21, 24, 27-28, 67-68 under 103(a) of Cass in view Herne. The response asserts that Cass does not teach or suggest the binding of disclosed dithiols and hairpin molecules "following expose of the fluorescence quenching surface to mixture comprising a ratio of space molecule to first molecule of about 5:1 or greater" as recited in claim 1. The response asserts that Cass fails to teach or suggest the critical need for the recited ratio of space to hairpin with recited fold increase in fluorescence. This response has been thoroughly reviewed and not found persuasive. The claims do not require the binding of dithiols and the claims require that a first and second region is complementary however the

claims does not require that a hairpin conformation is formed, the claims merely require that under appropriate conditions either a hairpin conformation is formed when the first and second region are hybridized OR a non-hairpin conform nation. Furthermore the rejection stated that Cass does not teach a plurality of spacer molecules that when mixed has a ratio of 5:1.

The response asserts that Herne does not overcome the deficiency of Cass. The response asserts that the claim language does not recite that a ratio of spacer: nucleic acid is about 5:1 or greater that exists on the substrate, the claim rather recites that the substrate is exposed to such a mixture. This response has been thoroughly reviewed but not found persuasive. It is noted that the claims are not drawn to methods, as appears to be asserted by applicant. The claims are drawn to a product and thus the examiner agrees that the product (substrate) does not necessarily have to have a 5:1 ratio of spacer: nucleic acid but that the product merely is required to have the recited function when exposed to a 5:1 ratio.

The response asserts that Herne merely teaches a method of removing excess nonspecifically bound DNA probes from the surface of the substrate and there is a significant different between the dissociation kinetics and binding kinetics of DNA probes to substrate and the difference is evidence when these two are compared in terms of probe distribution on the surface of the substrate. The response asserts that Herne does not involve exposing the surface to the recited mixture of agents. This response has been thoroughly reviewed but not found persuasive. As stated above the claims are drawn to a product not a process as such the claim merely requires that the substrate comprising a fluorescence quenching surface, a first nucleic acid molecule comprising a first and second end wherein the first end is bound to the surface, a first and second region complementary to the first region, a first fluorophore bound to the second

end, a plurality of spacer molecules bound tot eh fluorescence quenching. Thus, Herne teaches the substrate has spacer molecules with a ratio of 5:1 and thus it would have been obvious to modify the sensor ship of Cass with the spacer molecules of Herne.

The response asserts that one of skill in the art would have expected that the method of Herne would not have worked with hairpin probes because the folding and self assembly properties of hairpin DNA are very different from those of linear DNA probes. The response asserts that liner probes would adsorb much more readily to gold surfaces on the contrary to hairpin molecules. The response asserts that the charge density for a collection of hairpin molecules would behave differently under similar ionic conditions. This response has been thoroughly reviewed but not found persuasive. Both Herne and Casse teach nucleic acid probes attached to gold substrate. Herne teaches mercaptohexanol to remove nonspecifically absorbed DNA from the gold surface and teaches it is an important factor in maximizing hybridization efficiency (see pg. 8920, 2nd column), thus one of skill in the art would have expected that the use of MCH of Herne could work with any type of nucleic acid probe attached to a gold surface. The motivation to use MCH is not based on the type of probe attached to the gold surface but that MCH is used as a competitor to prevent nonspecific binding to the gold surface. Furthermore, even arguendo that the folding and self assembly properties of hairpin DNA are different than linear DNA, both Herne and Casse teach hybridization of nucleic acid probes attached gold surfaces and teach detection of hybridization by fluorescence, therefore both Herne and Casse teach the same mechanism (hybridization of target nucleic acids) and behavior (single stranded nucleic hybridizing to target) of nucleic acids to a gold surface.

The response asserts that the Miller declaration provides evidence that an expectation of success would have been lacking and that Herne does not overcome the deficiencies of Cass. The response asserts that the sensor chip synthesized using the optimal steps of Herne with hairpin probes of Cass does not afford a functional sensor chip. The response asserts that an exemplary sensor chip prepared for comparison using the same hairpin and target yield a 20 fold increase in intensity as opposed to the chip of Herne and Cass and thus there is no reasonable expectation of success. The declaration by Miller teach a thiolated hairpin probe using the protocol and optimal conditions in table 1 of Herne using 1 μM hairpin DNA with 1.0mM MCH for 60min. The declaration provides a direct comparison of the same type of substrate soaked in a mixture of 3 μM MP and 300nM hairpin probe a 10:1 ratio for 120 min. Both substrates were incubated overnight with target solution containing target molecule at concentration of 2.5 μM and fluorescence intensity measured. The declaration asserts that the sensor chip of Herne has a reduced post hybridization fluorescence intensity while the aver post hybridization intensity of the claimed sensor chip is 20 times more thus demonstrating that Herne method fails to provide a functional sensor chip, let alone a chip that has a 5 fold increase in intensity. This response and declaration has been thoroughly reviewed but not found persuasive. The declaration does not provide a direct comparison of the hybridization event of the two substrates. The concentration of the target to probe value is vastly different between the two substrates. The substrate of applicants has almost a 10:1 ratio of probe: target (.3 μM:2.5 μM) which can greatly enhance specificity and fluorescence whereas the substrate of Cass and Herne provided for by applicant is only a 2.5 fold difference (1 μM: 2.5 μM). Furthermore, the hairpin probe provided for in the declaration is not the hairpin probe disclosed by Cass. Cass exemplifies a 5' end with

fluorescein and a 3' end biotin group attached to a linker (See example 4 of Cass) and the sequence set forth in SEQ ID NO 1 and the target DNA is set forth in SEQ ID NO 2, which differs from the probe and target presented in the declaration. Thus the substrate and probe demonstrated in the declaration is not the substrate of Cass modified with the teaching of MCH of Herne and compared to the same probe and substrate, including concentration and hybridization conditions using the exemplified MP in the specification. Therefore the declaration is not found persuasive that a sensor chip of Cass modified with MCH is not functional as the declaration does not provide a teaching of Cass with MCH followed by binding of a target does not detect the target nucleic acid nor provide evidence that fluorescence will decrease. Furthermore, it is noted that the declaration is not commensurate in scope with the claims. The claims do not require a 10:1 fold ratio of probe: target nor do the claims require the use of MP, as demonstrated in the declaration to have a 5-fold increase in fluorescence intensity. Furthermore, it is noted that the specification teaches that competitor molecules (spacer molecule) contain a thiol group thereby allowing coupling of the competitor molecule to the fluorescence quenching surface and teach preferred competitor molecules include without limitation thiol-containing compounds, thus the specification demonstrates that any thiol containing compound will act as a spacer molecule (see pg. 19, lines 17-32), which is the same teachings of Herne. Herne teaches that MCH, a thiol containing compound, binds to the fluorescence quenching surface of the chip (See figure 4). Thus, the teachings of Herne are consistent with the teachings in the specification. Therefore, the declaration is not found persuasive and one of skill in the art would have had a reasonable expectation of success that

combing the substrate containing a hairpin bound probe with MCH would have yielded the claimed invention.

5. The response traverses the rejection of claims 12, 13, 22, and 23 under 35 USC 103(a). The response asserts that the combination of Cass and Herne and further in view of Bruchez does not demonstrate how Bruchez overcomes the above noted deficiencies of Cass and Herne. As stated above the rejection of Cass in view of Herne is maintained and therefore the rejection of claims 12, 13, 22, and 23 of Cass in view of Herne and further in view of Bruchez is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Sarae Bausch PhD/
Primary Examiner, Art Unit 1634